REMARKS

Claims 1 and 18 are currently pending in the application. Claim 1 is in independent form.

In response to the Notice of Non-Compliant Amendment, the claims in this Second Supplemental Amendment have been appropriately amended based on the First Supplemental Amendment filed on March 25, 2009, which was based on the Amendment filed on February 3, 2009, in response to the Office Action dated October 3, 2008. Therefore, the claims in the present amendment should be compared to those in the First Supplemental Amendment of March 25, 2009, and not another previous Amendment.

Support for the amended language in claim 1 can be found in [0067]-[0068] (i.e. double labeling). Claim 1 has been amended to clarify the invention. One skilled in the art knows that there are newly formed cells because of BrdU labeling. One can identify these newly formed cells by double labeling the cells, that is, using a marker of specific cell type, e.g. glial fibrillary activated protein (GFAP) which identifies astrocytes as well as stem-like progenitor cells, doublecortin, which identifies migrating neuroblasts, NeuN which identifies neurons, plus other markers such as MAP2, in combination with BrdU. No new matter has been added.

Claims 1, 6-8, and 14-17 stand rejected under 35 U.S.C. §112, second paragraph, because it is not clear what is meant by "administering a post ischemic event". In response thereto, Applicants have previously amended the claims to set "administering" apart from "post neuronal injury". Applicants have previously amended "post ischemic event" to "post neuronal injury" because the invention is applicable in many more instances wherein a patient requires neurogenesis, i.e. production of new neurons and new brain cells, than just

after an ischemic event. In other words, the administering step is performed after neuronal injury has occurred in a patient. Reconsideration of the rejection is respectfully requested.

Claims 1, 6-8, and 14-17 stand rejected under 35 U.S.C. § 102(b), as being anticipated by Endres, et al. Specifically, the Office Action holds that Endres, et al. teaches administering statins to patients for the treatment of ischemia and that HMG-CoA can reduce cerebral ischemia by up-regulating eNOS expression. The Office Action holds that the mechanistic functions affecting new neuron growth, increasing levels of cGMP, augmenting, and increasing neurological function will inherently occur once the drug is administered. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Endres, et al., as applied to the claims, is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

Endres, et al. only teaches administration before ischemia to protect against damage and does not disclose any new neuronal growth. See Results, emphasis added: "To determine whether statin administration confers protection against ischemic stroke, 129 /SV wild-type mice were s.c.-injected daily for 14 days with an HMG-CoA reductase inhibitor Sim (0.2, 2.0 and 20 mg/kg) ***before MCA occlusion***." In other words, the compounds in Endres, et al. are only used prophylactically. Furthermore, Endres, et al. gives statins only

as a "neuroprotective agent" with the intention of reducing the damage to the brain.

In contradistinction, the present invention requires administration post ischemic event, i.e. after stroke has already occurred. The method of the present invention is not a prophylactic method, but rather one that is a treatment for conditions that have already occurred. The present invention also administers statins as a neurorestorative agent, with the intention of producing new brain cells and promoting recovery of function. The brain damage is not in any way altered when treated with statins, since the present invention administers the agent at a time beyond which the agent can have a protective effect. Instead of treating damage as in Endres, et al., the present invention administers statins to treat intact tissue to compensate for the damage. Thus, Endres, et al. does not perform a critical step in the administration of the compounds of the present invention.

Furthermore, Endres, et al. does not disclose any new brain cells, i.e. the development of new brain cells through neurogenesis, as required by the independent claims and evidenced by the uptake of BrdU and identified by the double labeling, as shown in Figures 1-8B of the present application and described in detail in Example 1. The appearance of new brain cells does not inherently occur just because a similar compound is administered. Endres, et al. merely teach that HMG-CoA reductase inhibitors provide their benefit by increasing blood flow and reducing brain injury during cerebral ischemia. Increasing blood flow and reducing brain injury are irrelevant to the mechanism of the present invention. As Applicants have shown on multiple occasions, improvement of outcome and neurogenesis are independent of blood flow and lesion volume. Applicants demonstrate over again that neurogenesis and improvement of function occur when there is no change in brain injury and no change in blood flow. So, it is quite possible to see different mechanistic effects can result with similar compounds *and therefore*

these mechanisms are not necessarily inherent to the compounds. The work of Endres et al. implies therapeutic benefit only results from a reduction of lesion volume, which is counter to the findings of the present invention, and incorrect. One cannot in any way extrapolate from Endres, et al. that neurogenesis occurs and therapeutic benefit is present when HMG-CoA reductase inhibitors are administered post neuronal injury.

Therefore, since Endres, et al. does not disclose increasing the numbers of new brain cells as set forth in the presently pending independent claims, the claims are patentable over Endres, et al. and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8, and 14-17 stand rejected under 35 U.S.C. § 102(e), as being anticipated by U.S. Patent No. 6,423,751 to Liao. Specifically, the Office Action holds that Liao discloses up-regulation of endothelial cell nitric oxide synthase expression by administration of HMG-CoA reductase inhibitors such as atorvastatin for treatment post stroke. Liao teaches that a surprising connection was made in connection with the treatment of ischemic stroke when brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. Cerebral blood flow was better in the treated animals and it is believed that the positive results are attributable to the up-regulation of endothelial cell nitric oxide synthase activity. The Office Action holds that the other limitations recited in the claims are inherent to the compounds administered. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Liao, as applied to the claims, is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

The Liao patent merely discloses that stroke can be treated during a finite period of time. It is commonly known to those of skill in the art that there

is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Essentially, the Liao patent discloses treatment before or during the stroke itself in order to afford protection from stroke. ***Liao does not disclose treatment post neuronal injury***.

While Liao states that "the invention … is useful for treating subjects with hypoxia-induced conditions", there is no reason to interpret this statement to mean that treatment is given after stroke as it must be read in the context of the whole patent disclosure (col. 3, lines 45-46). While conditions caused by hypoxia can be treated, this treatment is given prior to any hypoxia-induced event. There is no indication from the Liao patent that treatment can be given post neuronal injury. Every example given by Liao is directed to prophylactic treatment before ischemia occurs, especially in Example 17 (simvastatin treatment for 14 days followed by production of cerebral ischemia).

Furthermore, nowhere in the Liao patent is there any statement or inference to neurogenesis (i.e. the generation of new neurons), recovery from stroke with treatment after such stroke has happened, or recovery of brain plasticity as required by the presently pending independent claim. Liao does not perform the required steps of labeling new brain cells with BrdU and therefore Liao cannot identify increased numbers of new brain cells by detecting BrdU labeled cells and double labeled cells.

Applicants previously presented a journal article by Liao (proc. Natl.

Sci. USA, Vol. 95, pp. 8880-8885, July 1998) to further provide evidence that Liao only discloses prophylactic treatment or at most treatment during a stroke. This article also examines the effect of HMG-CoA reductase inhibiting drugs on ischemia through their mechanism of up-regulating endothelial nitric oxide synthase. The goal of the article is "to determine whether statin administration confers protection against ischemic stroke" and therefore simvastatin was administered daily for 14 days to mice before MCA occlusion (p. 8881). Further, the authors state that "the major finding in this study is that prophylactic treatment with HMG-CoA reductase inhibitors protects against ischemic strokes after focal brain ischemia" (p. 8884). This article teaches much of the same methods and findings with simvastatin as the Liao patent. Accordingly, there is no motivation for treatment after the stroke is complete, i.e. post ischemic event, since this is a point in time substantially after the onset of the symptoms.

Therefore, since Liao does not disclose administration the compounds of the present invention post ischemic event or new neuron growth as set forth in the presently pending independent claims, the claims are patentable over Liao and reconsideration of the rejection is respectfully requested.

Claim 1 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Quast, et al. taken with Horackova, et al., in view of U.S. Patent No. 5,428,070 to Cooke, et al. Specifically, the Office Action holds that Quast, et al. teaches administering L-arginine (as N-monomethyl-L-arginine) to rats after ischemic stroke has occurred. Quast, et al. fails to teach identifying new neuron growth as required by the instant claim.

The Office Action holds that Horackova, et al. teaches more nitric oxide synthesizing neurons are present after the administration of a nitric oxide donor S-nitroso-N-acetylpenicillinamine implying new neurons are made, and the reference suggests SNAP augments neurons. Although Horackova, et al.

did not use L-arginine, SNAP is a nitric oxide donor, and the Office Action holds that substituting one for the other is within the purview of one skilled in the art because both are nitric oxide donors and would be expected to function the same.

The Office Action further holds that Cooke, et al. discloses administering L-arginine after vascular injury with emphasis on decreasing the effects of atherogenesis, and atherosclerotic vascular diseases such as stroke are higher in patients with non-insulin-dependent diabetes mellitus wherein the conditions may result in stroke. The Office Action holds that the drug L-arginine is administered after the injury (post) and cGMP is increased resulting in new neuron growth.

Thus, the Office Action holds that one skilled in the art would have been motivated to administer L-arginine to patients post stroke in order to promote neurogenesis, or growth of new neurons, because L-arginine is the substrate for nitric oxide (NO) production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. The Office Action further holds that it would have been obvious to one skilled in the art to combine the cited references and administer L-arginine in a post stroke event to a patient because the art teaches so and with regards to identifying increased numbers of new neurons, the teaching of Horackova, et al. indicates that more neurons are present since L-arginine increases the beating of myocytes. Reconsideration of the rejection under 35 U.S.C. §103(a) as being unpatentable over Quast, et al., Horackova, et al., and the Cooke, et al. patent is respectfully requested.

Quast, et al. has nothing to do with neurogenesis and recovery of function, especially by administering a NO donor. In fact, just the opposite is concluded from this reference: “In conclusion, we demonstrate for the first time that NO is an important mediator in hyperglycemic-exacerbated ischemic

brain injury. By inhibiting NO production, low dose L-NAME dramatically attenuates injury to the brain cells and to the cerebral vasculature". The study by Quast et al shows that an NOS inhibitor reduces ischemic cell damage, by reducing NO free radicals. In other words, Quast, et al. shows that inhibiting NO is beneficial for neural injury and that administering NO would only cause further damage in the brain. NO has a role in acutely after injury in potentially aggravating cell damage after in ischemic event. In contradistinction, the present invention demonstrates that NO donors and agents which increase NO and cGMP ***improve*** neurological function. From Quast et al, one would conclude the opposite and would not administer L-NAME to a patient. Quast, et al. also does not disclose increasing numbers of new brain cells, labeling new brain cells with BrdU, or detecting the BrdU labeled new brain cells or double labeling the cells as required by the presently pending independent claim.

Horackova, et al. investigates, in "culture", not *in vivo*, the interaction between cadiomyocytes and extracardiac and intrinsic cardiac neurons. The goal of this study is to determine the influence of these neurons on the beating frequency of the cardiac cells (myocytes). The conclusions of the study are 1) that NO sensitive neurons increase the beating rate of cardiomyocytes in the presence of NO; 2) more NO synthesizing neurons are present in intrinsic cardiac neurons versus extrinsic neurons; and 3) the beating rate of non-innervated myocyte cultures is not directly affected by NO.

Horackova, et al. has absolutely nothing to do with neurogenesis or recovery of brain function. Horackova, et al. simply demonstrates that certain types of peripheral nerve cells can affect the beating of cardiac cells and that NO sensitive neurons alter the beating rate of heart cells. There is no logical or scientific connection between this study and the generation of new neurons, much less neurons within the subventricular zone of the brain. No new brain cells are generated in Horackova, et al.'s *in vitro* study using

peripheral nerves. The data and conclusions are limited to the effect of NO sensitive neurons on the beating rate of cardiomyocytes.

In addition, the statement that, "Horackova... teaches more NO synthesizing neurons are present after the administration of a NO donor SNAP, implying new neurons are made" is an incorrect reading of the text. ***No neurons are made, the results show only that there are more NO sensitive neurons within the heart than outside the heart, i.e. Stellate ganglion neurons.*** Also, the statement that "SNAP augments neurons" is incorrect. See the first paragraph of the Discussion in Horackova, et al., "SNAP … enhanced the beating rate of myocytes… This indicates the presence of NO sensitive neurons in these co cultures". The statement by the Office Action that "quantities of neurons in different sites were compared", is also a misunderstanding of the Horackova, et al. text. Horackova, et al. note that more cardiac neurons are NO reactive than non-cardiac peripheral neurons; there is no change in the quantity of neurons, just that neurons within the cardiac muscle are somewhat different than neurons outside the cardiac muscle - they are NO sensitive and respond to agents like SNAP or L-Arginine. Thus, in contradistinction to the present invention, Horackova, et al. does not teach the production of new brain cells, labeling the new brain cells with BrdU, and detecting BrdU labeled cells or double labeling the cells.

The Cooke, et al. patent explicitly addresses the role of administering L-arginine as a substrate for nitric oxide (NO) in the treatment of atherosclerosis and restenosis. Although atherosclerosis is a minor risk factor for stroke, the reduction of atherosclerosis or restenosis of a coronary artery or even a cerebral artery (which is not the focus of the Cooke, et al. patent) has nothing to do with neurogenesis, brain plasticity, and inducing recovery from stroke as in the presently pending application.

The basic chemistry of the NO pathway dictates that cGMP is

increased in response to NO. Therefore, administering a NO substrate will, based on the laws of chemistry, increase cGMP. In example 2 of the Cooke, et al. patent, column 9, line 22, the text reads, "the reduction in platelet aggregation was associated with a two-fold increase in cGMP content in aggregated platelets from arginine treated animals". This is simple chemistry, that a substrate for NO will increase cGMP. There is, however, no statement or logical scientific connection that can be made relating cGMP to the induction of neurogenesis and recovery from stroke, as claimed by the presently pending independent claims. Nowhere in the Cooke, et al. patent, is there any statement or inference to the brain, to neurogenesis, to recovery from stroke and brain plasticity. Certainly Cooke, et al. does not disclose or suggest the presently added step to claim 1 of "identifying increased numbers of new brain cells". One cannot infer in any way that a decrease in atherosclerosis and restenosis of a vessel is related to the production of new brain cells. The statements in the Cooke, et al. patent in column 3, lines 52-53 address the role of arginine and NO in restenosis, completely independent of neurogenesis, stroke, and recovery. This is a vascular issue about vessels that re-occlude and the rate of re-occlusion is reduced with these compounds. Likewise, the reference to col.9, lines 22-24, relates to the role of NO/L-arginine on aggregated platelets; again, not in anyway associated with the presently pending independent claims. The Cooke, et al. patent is directed towards a means to reduce vascular pathology, associated with atherosclerosis and re-occlusion of blood vessels. The presently pending claims are independent of vascular issues, and as discussed in the previously submitted Declaration, Applicants have also shown that agents which increase cGMP such as PDE5 inhibitors and statins act directly on neurons and progenitor cells in brain to induce the production of new brain cells.

None of the cited references teach the production of new brain cells through the administration of the compounds of the present invention, nor the labeling or detection of these new brain cells with BrdU or the double labeling

of cells. This function is not inherent in the compounds and not inherently disclosed or suggested in the cited references. Furthermore, Quast, et al. teaches away from the administration of NO donor compounds. Therefore, neither Quast, et al., Horackova, et al., or Cooke, et al. alone or in combination teach the required steps of the presently pending claims of producing new brain cells and identifying new brain cells.

Since neither the cited reference alone or in combination with knowledge in the art suggests the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke, et al. patent taken with the Liao patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference, further in view of Quast, et al. taken with Horackova, et al. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke, et al. patent taken with the Liao, patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference, further in view of Quast, et al. taken with Horackova, et al. is respectfully requested.

As stated above, the Cooke, et al. patent does not disclose or suggest the present invention because there is no disclosure or suggestion of neurogenesis or increased neural function with the administration of the compounds along with identifying increased numbers of new neurons as required by the presently pending independent claims. Further combining Cooke, et al. with the above cited references does not arrive at the present invention.

The Office Action has held that the Liao patent teaches a surprising connection was made in connection with the treatment of ischemic stroke, wherein brain injury reduction is measured by determining a reduction in the infarct size in treated versus control groups. At column 8, lines 62-65 there is further disclosed that the "brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups." In other words, the treatment is similar to that of the Moskowitz patent previously cited in the present application, which does not provide the same results as accomplished by the method of the presently pending claims.

Contrary to the statement that "L-arginine is known for its properties of promoting neurogenesis (see Moskowitz, of record)" made by the Office Action, Applicants have previously stated that Moskowitz discloses no such thing and in fact makes the statement that neurons cannot regenerate. Applicants note that no cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, *none of the cited prior art can perform the required steps of claims 1 and 6-8 of "identifying increased numbers of new neurons"*. Further with respect to the statement made by the Office Action, Applicant has included new claims 14-17 which do not recite the compound "L-arginine". Moskowitz does not disclose any evidence that L-arginine can be effective after an ischemic event, and Moskowitz does not disclose the other compounds recited by the claims even capable of being used to treat after an ischemic event.

As was found with regard to the Moskowitz patent, the Liao patent merely discloses that stroke can be treated during a finite period of time. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated.

Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Essentially, the Liao patent discloses treatment before or during the stroke itself in order to afford protection from stroke.

While Liao states that "the invention … is useful for treating subjects with hypoxia-induced conditions", there is no reason to interpret this statement to mean that treatment is given after stroke as it must be read in the context of the whole patent disclosure (col. 3, lines 45-46). While conditions caused by hypoxia can be treated, this treatment is given prior to any hypoxia-induced event. There is no indication from the Liao patent that treatment can be given post neuronal injury. Every example given by Liao is directed to prophylactic treatment before ischemia occurs, especially in Example 17 (simvastatin treatment for 14 days followed by production of cerebral ischemia).

Furthermore, nowhere in the Liao patent is there any statement or inference to neurogenesis (i.e. the generation of new neurons), recovery from stroke with treatment after such stroke has happened, or recovery of brain plasticity as required by the presently pending independent claim. Liao does not perform the required steps of labeling new brain cells with BrdU and therefore Liao cannot identify increased numbers of new brain cells by detecting BrdU labeled cells or double labeling cells.

Applicants previously presented a journal article by Liao (proc. Natl. Sci. USA, Vol. 95, pp. 8880-8885, July 1998) to further provide evidence that Liao only discloses prophylactic treatment or at most treatment during a

stroke. This article also examines the effect of HMG-CoA reductase inhibiting drugs on ischemia through their mechanism of up-regulating endothelial nitric oxide synthase. The goal of the article is "to determine whether statin administration confers protection against ischemic stroke" and therefore simvastatin was administered daily for 14 days to mice before MCA occlusion (p. 8881). Further, the authors state that "the major finding in this study is that prophylactic treatment with HMG-CoA reductase inhibitors protects against ischemic strokes after focal brain ischemia" (p. 8884). This article teaches much of the same methods and findings with simvastatin as the Liao patent. Accordingly, there is no motivation for treatment after the stroke is complete, i.e. post ischemic event, since this is a point in time substantially after the onset of the symptoms.

With regard to the Kaposta, et al. and Ohtsuka, et al. references, these references merely disclose use of compounds prophylactically. There is no disclosure for the use of the compounds post ischemic event for creating neurogenesis.

With regard to Quast, et al. and Horackova, et al., as stated above, Quast, et al. teaches away from using NO donors in the first place. Horackova, et al. has nothing to do with neurogenesis and merely teaches that cardiomyocytes are sensitive to NO and beat faster in the presence of NO, and that there are more NO sensitive neurons in cardiac tissue than outside.

Applicants note that none of the cited references disclose any evidence of the production of new neurons and the identification of new neurons.

Since none of the cited references alone or in combination with one another suggest the currently claimed invention, it is respectfully submitted

that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8, and 14-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Jeremy, et al. and Poluha, et al., in view of U.S. Patent No. 6,423,751 to Liao. Specifically, the Office Action holds that Jeremy, et al. teach that sildenafil increases cGMP and also may enhance erection by augmentation of nitric oxide mediated relaxation pathway, thus affecting new neuron growth in a patient and augmenting the production of neurons. The Office Action holds that Poluha, et al. teaches a nitric oxide donor NGF increasing levels of cGMP, that results in neurite extension.

The Office Action also holds that Liao teaches up-regulation of endothelial cell nitric oxide synthase expression by administration of HMG-Co reductase inhibitors for the treatment of stroke. Liao teaches a surprising connection was made in the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. The Office Action holds that Liao fails to teach neuron growth and identifying increased numbers of new neurons. However, based on the teaching from the background section indicating that in mammals nitric oxide is expressed in neurons of nitric oxide synthase and are expressed in endothelial cells of nitric oxide synthase. Thus, the Office Action holds that one skilled in the art would know that nitric oxide is responsible for neurogenesis.

Jeremy, et al. discloses that enhanced penile erection produced by PDE5 inhibitors is mediated by vaso-relaxation and increases in blood volume, events which have absolutely nothing to do with the increase in neurogenesis. The mechanism by which sildenafil treats erectile dysfunction is by altering blood volume and vascular constriction, ***not by the production***

of new brain cells. ***No new brain cells are detected through BrdU labeling by Jeremy, et al.*** Sildenafil increases erection within minutes-hours. Neurogenesis as in the present invention occurs in a time scale of days. Jeremy, et al. teaches that sildenafil increases cGMP, and this is well known about sildenafil since increased cGMP is intrinsic to the design of sildenafil as a PDE5 inhibitor.

Jeremy, does not disclose administering the compounds of the present invention to increase neurogenesis (which occurs through increasing cGMP). There is no reason to believe that the results of the present invention are inherent to the compounds as discussed above. Jeremy, et al. also does not administer the compounds post ischemic event.

Poluha, et al. disclose that NO is a regulatory molecule that influences that "perhaps" include neuronal proliferation and differentiation. NO activates a promoter and is required for NGF-induced expression of two markers associated with neuronal differentiation, i.e. change in phenotype of the cells to affect neurite extension. It is well known that neurotrophins such as NGF increase neurite expression cell systems; however, ***neurite extension is NOT the production of new brain cells***. Nitric oxide itself is not an NGF. Poluha, et al. teaches a linear pathway by looking at how NGF affects neurite outgrowth via a cell signaling pathway. There is no reason to believe that new neurons can be generated from the compounds of the present invention based on Poluha, et al.

As stated above, Liao does not disclose the required steps of the present invention, either alone or in combination with other cited references. No other references besides Applicants' own work have demonstrated that neurogenesis (i.e. production of new neurons) is even possible with the administration of NO donor compounds of the present invention. One skilled in the art would not have identified that NO donor compounds can be used to

produce new neurons because this result has simply never been shown before Applicants' showing. The Office Action is using an incredible amount of hindsight to make its conclusions, but if this property was inherent to NO donor compounds, Applicants' result would have been found in some other reference.

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

"It is essential that 'the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made … to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.'" *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983)).

Therefore, since Jeremy, et al, Poluha, et al., and Liao alone or in combination with knowledge of one skilled in the art do not disclose the required elements of the pending claims of the present invention, the present invention is patentable over Jeremy, et al., Poluha, et al., and Liao and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8, and 14-17 of this application have further been rejected as unpatentable based on provisional non-statutory obviousness-type double patenting over co-pending Application No. 10/500,694. These rejections can be readily overcome by the filing of a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) or (d). Applicants stand ready to provide the appropriate terminal disclaimer upon the indication of the allowance of the pending claims.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In conclusion, it is respectfully submitted that the presently pending claims are in condition for allowance, which allowance is respectfully requested. Applicant respectfully requests to be contacted by telephone if any remaining issues exist.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC

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Dated: June 29, 2009

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

Date of Electronic Filing: June 29, 2009

I hereby certify that this correspondence is being electronically filed with the United States Patent & Trademark Office on the above date.

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